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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/632,657	08/04/2000	Gordon Duff	MSA-012.01	2287

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,657	DUFF ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,22-24,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-12, 22-24, 43, and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed December 27, 2002. Applicants arguments and amendments have been fully considered but do not overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. Applicant's election with traverse of group I, claims 1, 5-12, 22-24, 43 and 44 in Paper No. 11 is again acknowledged. As previously discussed, the restriction requirement between the linked inventions is subject to the nonallowance of the linking claims 11, 22, 23 and 43. For the reasons discussed below, the linking claims are not allowable. Accordingly, the restriction requirement is maintained. As set forth in the previous Office action, claims 11, 22, 23 and 43 have been examined as linking claims, and the remaining claims have been examined with respect to the IL-1RN (+2018) polymorphism and with respect to SEQ ID NO: 7 and 8.

3. Claims 1, 5-12, 22-24, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether an individual of Northern-European descent is predisposed to early onset menopause by detecting the presence of IL-1RN (+2018) allele 2 as indicative of a predisposition to early onset menopause, does not reasonably provide enablement for methods which determine a predisposition to early onset menopause in non-Northern European women by detecting IL-1RN(+2018) allele 2 or methods for detecting early onset menopause by detecting any other IL-1 alleles or haplotypes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1 and 5-10 are drawn to a method for determining whether a subject is predisposed to having early onset menopause by detecting the presence of an IL-1RN (+2018) allele 2 as predictive of the subject's predisposition to early onset menopause. Claims 11-12 are drawn to a method for determining a subject's susceptibility to early onset menopause by detecting any IL-1 haplotype associated with early onset menopause. Claims 22-24 are drawn to methods for identifying an allelic pattern associated with early onset menopause by identifying a first allele in linkage disequilibrium with a second allele that is associated with early onset menopause. Claims 43 and 44 are drawn to methods for determining a subject's predisposition to early onset menopause by detecting an allele within the 44112332 haplotype.

The specification (pages 60-61) teaches that in women of European descent, the presence of IL-1RN (+2018) allele 2 was found to be associated with early onset menopause. However, in women of non-European descent, the presence of IL-1RN (+2018) allele 2 was found to be associated with **later** onset of menopause, with the effect increasing with each copy of allele 2. Accordingly, the specification has not enabled methods which determine susceptibility to early onset menopause in women of non-European descent by detecting the presence of IL-1RN (+2018) allele 2. Further, the specification does not teach any additional alleles, either IL-1 alleles or non-IL-1 alleles that are associated with early onset menopause. The claims are inclusive of detecting a polymorphism in any gene as indicative of early onset menopause. The showing of one polymorphism associated with early onset menopause in one ethnic groups is clearly not representative of a genus of all possible polymorphisms in any gene that may be associated with

early onset menopause. Extensive, trial and error experimentation would be required to examine additional genes for the presence of a polymorphism associated with early onset menopause. The specification does not provide any guidance as to how to identify any non-IL-1 genes that are associated with early onset menopause without undue experimentation. Regarding the claims as they are limited to methods which diagnose early onset menopause by detecting other IL-1 alleles, the specification does not teach any alleles other than IL-1RN (+2018) which are associated with early onset menopause in women of European descent. While the specification postulates that alleles in linkage disequilibrium with the IL-1RN (+2018) allele 2 could also be used to diagnose early onset menopause, given the fact that other alleles are not in 100% linkage disequilibrium with the stated alleles and that stated alleles have variable frequencies of association with early onset menopause, it is highly unpredictable as to whether alleles in linkage disequilibrium with of IL-1RN (+2018) allele 2 or any other IL-1 allele would be sufficiently correlated with the occurrence of early onset menopause. Further, while the specification suggests that IL-1 genotypes association with inflammation may be used to diagnose any disease that involves inflammation, Applicants have not provided sufficient evidence to establish that any level of inflammation or any inflammatory response in women is correlated with early onset menopause.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a

reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only 1 allele in one IL-1 gene out of all possible IL-1 genes and all possible non-IL-1 genes has exemplified the use of only this one allele (i.e., IL-1RN (+2018) allele 2) as a means for diagnosing a predisposition to early onset menopause Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and other genes for additional alleles which may be analyzed for their association with early onset menopause. Additionally, the results set forth in the specification clearly demonstrate the unpredictability in the art since the findings obtained with non-European women were directly opposite of those obtained with European women. The unpredictability in the art of establishing a correlation between a polymorphism and a particular disease is further highlighted by the teachings of Langdahl et al (Journal of Bone and Mineral Research (2000) 15: 402-4140. Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequency at which alleles are inherited. The reference also teaches that while one group reported that the repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3954) polymorphism, Langdahl et al were unable to

show linkage between these polymorphisms. Again, these teachings demonstrate the unpredictability of using an allele in linkage disequilibrium with a second allele as a means for diagnosing susceptibility to disease. With respect to claims 22-24, the broadest reasonable interpretation of these claims indicates that the claims are inclusive of methods which identify novel alleles associated with early onset menopause. While the specification is enabling for methods for detecting IL-1RN (+2018) allele 2 as indicative of an increase susceptibility to early onset menopause in women of European descent, the specification is not enabling for methods which search for novel alleles that may be in linkage disequilibrium with IL-1RN (+2018) allele 2.

To make and use an invention requires that the invention have a "real world" use. However, uses that require carrying out further research do not constitute a real world use. Thus, the specification has not adequately enabled methods which search for novel alleles associated with early onset menopause. Accordingly, in view of the lack of information in the specification as to how to reasonably identify other IL-1 alleles associated with early onset menopause without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a specific condition, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the response of December 27, 2002, Applicants traversed this rejection by stating that the claims have been amended to indicate that the presence of IL-1RN (+2018) allele 2 in Northern European women is indicative of early onset menopause and that the presence of IL-

1RN (+2018) allele 1 in non-Northern European women is predictive of a predisposition to early-onset menopause. However, this amendment to the claims does not overcome the present grounds of rejection because the specification does not in fact teach that the presence of IL-1RN (+2018) allele 1 is indicative of predisposition to early-onset menopause. The specification (page 61) teaches that the average age on onset of menopause in a UK study group was 49.3 years of age. The specification also teaches that in a US study population, women of Northern European descent having IL-1RN (+2018) allele 2 had an earlier onset of menopause by .96 years per copy of allele 2. In this same study, US women of non-Northern European descent having IL-1RN (+2018) allele 2 had a later onset of menopause by 1.16 years. The finding that women of non-Northern European descent carrying allele 2 had a later onset of menopause does not lead to the conclusion that the remaining women having allele 1 were predisposed to early onset menopause. The specification (page 10) defines early onset menopause as referring to "a premature menopause, that is, onset of menopause before that time at which menopause normally occurs." Accordingly, while the women of non-European descent having allele 1 may be characterized as having an earlier onset of menopause relative to the women of non-European descent having allele 2, this is not the same as indicating that the women of non-European descent having allele 1 are predisposed to early onset menopause (i.e., an early onset of menopause relative to the average age of onset of menopause).

Applicants state that claims 22-24 have been amended to "specifically reflect the IL-1 gene polymorphisms supported in the instant application." However, claims 22 and 23 do not recite any

particular polymorphisms. Rather, claims 22 and 23 are broadly drawn to identifying a second IL-1 allelic pattern that is in linkage disequilibrium with any first IL-1 allelic pattern associated with early-onset menopause. The specification has taught only 1 allelic pattern associated with early onset menopause in women of Northern European ancestry, namely IL-1RN (+2018) allele 2. Further, as discussed in the above rejection, the concept of searching for novel IL-1 allelic patterns in linkage disequilibrium with either defined or undefined IL-1 allelic patterns constitutes a research project. It is highly unpredictable as to what would be the identity of the first or second allelic pattern and one can only identify novel IL-1 allelic patterns through extensive, trial-by-error experimentation. Such experimentation is considered to be undue.

Applicants argue that it is not necessary to provide working examples for all embodiments of the claims and cite *In re Strahilivitz* in support of this argument. It is first noted that the Office action did not require that Applicants provide working examples for each embodiment of the claimed invention. Secondly, the facts of *In re Strahilivitz* are distinct from those herein. In the present application, the unpredictability in the art of identifying novel alleles in linkage disequilibrium with other alleles, of using alleles that are somewhat linked to another allele as a means of diagnosing disease and of identifying alleles diagnostic of disease is well established. Again, this unpredictability is demonstrated by the teachings of the present application in which completely opposite results were obtained with 2 different ethnic populations. The specification fails to provide any guidance as to how one might determine the effect of one's ancestry on the association between additional IL-1 alleles and the occurrence of early onset menopause.

Applicants dismiss the examiner's statements regarding the teachings of Langdahl in which Langdahl teaches that there is considerable variation between the frequency at which alleles in linkage disequilibrium are inherited. Applicants go on to remind the examiner that when a specification has been found enabling for its entire scope, the scope of the claims cannot be rendered non-enabling by virtue of later developments in the art. This argument is not persuasive because Applicants specification is in fact not enabling for the full scope of the invention claimed. The Langdahl reference was cited only to support what was already well established in the art--that is, that the use of alleles in linkage disequilibrium to diagnose disease is highly unpredictable. The concept that linkage is population dependent and that there is considerable variation between the frequency at which alleles are inherited is not a new concept, and certainly not a concept that was first determined after the filing of the present application. Applicants also cite Cox as establishing the predictability of using any allele in linkage disequilibrium as a means for diagnosing disease. However, Cox teaches only methods for identifying alleles in linkage disequilibrium, but does not establish that such alleles can be predictably used to diagnose disease. Cox (page 1186) states that "an understanding of which markers are in strong linkage disequilibrium allows for the more rational design of genetic studies. In the IL-1 system in particular, where alleles of different IL-1 genes may act in concert to determine an overall inflammatory phenotype, a knowledge of the existing disequilibria is vital to our understanding of which allele combinations are important in disease." Thus, while Cox teaches that identifying alleles that are in linkage disequilibrium will allow one to perform additional research to determine

which alleles or combination of alleles are associated with disease, the reference does not establish that any single member of a group of alleles in linkage disequilibrium can be used to diagnose disease based on the knowledge that one member of that group is associated with a disease in one population of individuals.

5. The terminal disclaimer filed on December 27, 2002 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,268,142 has been reviewed and is accepted. The terminal disclaimer has been recorded.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

June 18, 2003

CARLA J. MYERS
PRIMARY EXAMINER